Erectile Dysfunction Medications and Skin Cancer: An Analysis in US Veterans

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OBJECTIVE To examine the relationship between phosphodiesterase 5 inhibitor drugs (PDE5i) and skin cancers in a large-scale study of Veterans.

METHODS This was a retrospective database review using the Department of Veterans Affairs Informatics and Computing Infrastructure database. Veterans Affairs Informatics and Computing Infrastructure was searched 19 years for Veterans who received PDE5i treatment of erectile dysfunction. A non-PDE5i group of Veterans was selected for comparison analysis. Follow-up time, outpatient clinic visits and incidence of malignant melanoma (MM), and basal cell carcinoma (BCC) were measured in both groups.

RESULTS A total of 2.55 million Veterans were included in this study (1.27 million in each group). Mean age of the PDE5i group and non-PDE5i group was 59.2 years (standard deviation [SD] ± 10.8) and 58.7 (SD ± 10.8), respectively. Mean follow-up time for the PDE5i group was 8.9 years (SD ± 4.2) and 8.5 years (SD ± 4.3) for non-PDE5i group. Odds ratio for malignant melanoma and BCC in the PDE5i group was 1.25 (confidence interval 95%, 1.22-1.28, $P < .0001$) and 1.49 (confidence interval 95%, 1.46-1.51, $P < .0001$), respectively. PDE5i users showed more mean outpatient visits/year (8.9 SD ± 9.50) compared to non-PDE5i users (5.9 SD ± 10.0; $P < .0001$).

CONCLUSION Veterans prescribed PDE5is to treat erectile show a minimal increased risk of MM and a greater risk of BCC compared to non-PDE5i users. PDE5i users visited outpatient VA clinics at a higher rate than non-PDE5i users in this study. These findings suggest confounding variables are likely involved in the relationship between skin cancers and PDE5i use. PDE5i drugs remain a safe treatment for erectile dysfunction. UROLOGY 126: 116–120, 2019. Published by Elsevier Inc.

Erectile dysfunction is a common condition affecting more than 30% of men in the United States.[1] Phosphodiesterase Type 5 inhibitors (PDE5is) such as sildenafil, tadalafil, and vardenafil are the most commonly used drugs to treat erectile dysfunction. These drugs revolutionized the treatment of erectile dysfunction after the FDA first approved sildenafil in 1998, followed by vardenafil and tadalafil in 2003. Other indications for use of PDE5is include treatment of pulmonary hypertension[2] and benign prostate hyperplasia.[3] The safety profile of these drugs is excellent and the main contraindication to their use is concomitant use of nitrates.[4]

In vitro laboratory evidence demonstrated BRAF mutations downregulate Phosphodiesterase Type 5.[5,6] The BRAF V600 mutation is a significant factor in the development of malignant melanoma (MM), and is present in around 50% of cases of melanoma.[7] Given BRAF's importance in MM, studies began to explore the possibility that PDE5is could increase the development and invasiveness of MM in vivo. A prospective cohort study in 2014 by Li et al showed an increased hazard ratio (HR) of greater than 2 of developing MM with sildenafil use.[8]

Since the Li study, several other investigators showed smaller increases in MM risk among men using PDE5i drugs.[9-13] Some studies showed no evidence of causality, especially when examining the dose response involving the number of prescriptions or pills.[10,11] Studies showing an increased risk of MM with increasing number of prescriptions reported a very modest effect.[9,12] Similarly, there is no evidence for a biological gradient since higher stages of MM have yet to be associated with PDE5i use.[13] Nevertheless, considerable attention from the medical and scientific community arose when PDE5i drugs were added to the Food and Drug Administration Watch List in 2016 after several studies suggested an increased risk of developing MM with this class of drugs.[14]

Since most previous studies relied on small datasets, subsequent meta-analyses followed seeking to increase the

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power of the association. These meta-analyses showed similar levels of association between PDE5i use and MM.[13,15,16] To further study this reported relationship, we examined the incidence of MM in a large group of Veterans with a diagnosis of erectile dysfunction who were prescribed PDE5i drugs compared to Veterans who had no record of PDE5i prescriptions in the VA healthcare system. We also examined the incidence of BCC in PDE5i users and nonusers since the work of other investigators has suggested and increased risk of BCC in PDE5i users.[10]

MATERIALS AND METHODS

The study was approved by the Institutional Review Board of the Lexington VA Medical Center (IRB#: PRE-17-005-HE). We queried the VA Informatics and Computing Infrastructure (VINCI) database, a large data repository containing information from the VA electronic medical record. The study was a retrospective design comparing Veterans with a diagnosis of erectile dysfunction and taking PDE5i to Veterans with no record of PDE5i use in the VA system. The incidence of MM and BCC was measured and compared in each group. VINCI was searched from October 1998 to September 2017.

Inclusion and Exclusion Criteria for PDE5i Users

Male Veterans, aged 18-99 years, who had received PDE5i prescriptions (sildenafil, vardenafil, tadalafil, and avanafil) and had a documented diagnosis of erectile dysfunction, were selected from the VINCI database. To be included in the PDE5i group, the Veterans had no preexisting diagnosis of MM or BCC and no diagnosis of MM or BCC for at least 1 year prior to inclusion. Diagnosis codes for MM and BCC and were taken from International Statistical Classification of Diseases and Related Health Problems (ICD). VINCI was searched for ICD 9 and 10 diagnosis codes of MM and BCC of the skin, on the face, head, trunk, and extremities in the PDE5i drug group. Melanoma in situ codes were created after September 30, 2015 with the implementation of ICD-10. Prior to this date in ICD-9, melanoma in situ was captured under code 172.9 (MM of skin, not otherwise specified). For this group, MM and MM in situ were combined in the analysis and are subsequently referred to as MM.

Inclusion and Exclusion Criteria for Comparison Group, non-PDE5i Users

Male Veterans, aged 18-99 years, who had no record of receiving PDE5i prescriptions in the VA Healthcare system were selected as non-PDE5i users and matched 1:1 by race, age, and geography (most frequently used VA facility) to PDE5i users. Non-PDE5i users had no pre-existing diagnosis of MM or BCC and could not have a diagnosis of MM or BCC for at least one year before selection. VINCI was searched for ICD 9 and 10 diagnosis codes of MM and BCC of the skin in the non-PDE5i group as reported above for the PDE5i group.

Other Measured Variables

The frequency of outpatient VA clinic visits was measured in both groups. Total pills dispensed for all PDE5i users with a diagnosis of erectile dysfunction were measured. PDE5i users were subdivided and analyzed by quartiles of total pills dispensed, and odd ratios for MM and BCC were calculated for each quartile.

Statistical Methods

Data analysis: Demographic variables are reported as mean ± standard deviation or median (range). Since PDE5i users and non-PDE5i users were matched by age, race, and geographic location (most commonly used VA facility), raw odds ratios (OR) were calculated for MM and BCC. All statistical analyses were conducted using R Core Team (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).[17] OR and 95% confidence intervals were calculated using the Epidemiology Tools R package.[18] Statistical significance was calculated using chi-square tests, and defined as $P < .05$. PDE5i users were divided in quartiles according to PDE5i total pill counts for the entire study period and appropriate matched non-PDE5i users were selected for OR analyses.

RESULTS

Population Demographics

A total of 2,548,548 million Veterans were included in this study. There were 1,274,274 million in each group. Study group demographics are shown in Table 1. The majority were classified as white (64.5%) with blacks representing 22% of the cohort. Hispanics represented 5.7% of the study population and the remaining racial classifications were 3.1% or less. The mean age

Table 1. Demographics for PDE5i users and non-PDE5i users

Race	PDE5i Users	Non-PDE5i Users	Total (Percentage of Sample)
White	821,837	821,837	1,643,674 (64.5%)
Black	280,117	280,117	560,234 (22%)
Hispanic	73,114	73,114	146,228 (5.7%)
Non-Hispanic	38,910	38,910	79,820 (3.1%)
Unknown race	27,984	27,984	55,968 (2.2%)
Multi race	10,055	10,055	20,110 (0.8%)
Native Hawaiian or Pacific Islander	8156	8156	16,312 (0.6%)
Asian	7764	7764	15,528 (0.6%)
Native American or Alaskan Indian	6337	6337	12,674 (0.5%)
Total	1,274,274	1,274,274	2,548,548
Mean age years (±SD)	59.2 (±10.8)	58.7 (±10.8)	
Median age years (range)	60 (18-99)	59 (18-99)	
Mean follow-up years (±SD)	8.9 (±4.2)	8.5 (±4.3)	
Mean outpatient visits/year (±SD)	8.9 (±9.50)	5.9 (±10)	

Table 2. Malignant melanoma (MM) incidence by total pill count quartiles

		No MM (N)	MM (N)	OR (95% CI)	*P* Value
Total study population	*No PDE5I*	1,262,748	11,526		
	PDE5I	1,259,886	14,388	1.25 (1.22-1.28)	*P* < .0001
PDE5I pill quartiles					
First	*No PDE5I*	316,192	3078		
(1-14)	*PDE5I*	314,911	4539	1.42 (1.36-1.49)	*P* < .0001
Second	*No PDE5I*	319,341	2778		
(15-48)	*PDE5I*	317,906	4213	1.52 (1.45-1.60)	*P* < .0001
Third	*No PDE5I*	307,444	2804		
(49-132)	*PDE5I*	306,759	3489	1.25 (1.19-1.31)	*P* < .0001
Fourth	*No PDE5I*	312,684	2795		
(133-20592)	*PDE5I*	313,205	2274	0.81 (0.77-0.86)	*P* < .0001

Table 3. Basal cell cancer (BCC) incidence by total pill count quartiles

		No BCC (N)	BCC (N)	OR (95% CI)	*P* Value
Total study population	*No PDE5I*	1,241,479	32,795		
	PDE5I	1,226,138	48,136	1.49 (1.46-1.51)	*P* < .0001
PDE5I pill quartiles					
First	*No PDE5I*	310,495	8775		
(1-14)	*PDE5I*	307,673	11,597	1.33 (1.30-1.37)	*P* < .0001
Second	*No PDE5I*	313,821	8298		
(15-48)	*PDE5I*	310,248	11,871	1.45 (1.41-1.49)	*P* < .0001
Third	*No PDE5I*	302,422	7826		
(49-132)	*PDE5I*	298,697	11,551	1.49 (1.45-1.54)	*P* < .0001
Fourth	*No PDE5I*	307,737	7742		
(133-20592)	*PDE5I*	302,614	12,865	1.70 (1.64-1.74)	*P* < .0001

of the PDE5i group was 59.2 years and the non-PDE5i group was 58.7 years. The mean follow-up time for the PDE5i group was 8.9 years and 8.5 years for non-PDE5i user group. PDE5i users showed more mean outpatient visits/year (8.9 visits/y) compared to non-PDE5i users (5.9 visits/y; *P* <.0001)

Overall Incidence of MM and Basal Cell Cancer in PDE5i Users and non-PDE5i Users

During the study period, MM occurred in 14,388 Veterans who received PDE5i drugs and 11,526 Veterans who were non-PDE5i users (Table 2). During the same study period, BCC occurred in 48,136 Veteran PDE5i users and 32,795 Veteran non-PDE5i users (Table 3).

The OR for MM in the PDE5i group was 1.25. The OR increased slightly in the first 2 quartiles of lower volume PDE5i users (1.42 and 1.52), stayed the same in the third quartile (1.25), but decreased in the fourth quartile of highest volume PDE5i users (0.81) (Table 2). The OR for BCC in the PDE5i group was 1.49 and increased in each increasing quartile of PDE5i pill use to an OR of 1.70 for BC in the highest quartile users (Table 3).

COMMENT

Our results suggest PDE5i use in Veterans slightly increases the risk of MM. The risk of BCC in Veterans using PDE5is appears to be higher than MM. Interestingly, PDE5i users showed nearly double the rate of outpatient clinic VA clinic visits as non-PDE5i users.

Our findings of increased risk for developing skin cancers in Veterans receiving PDE5i drugs are similar to those of other investigators.[8-13] Loeb et al performed a retrospective analysis of 4065 Swedish men diagnosed with MM and reported a modest increase in risk of MM (OR 1.21) and basal cell carcinoma (OR 1.19) with PDE5i use.[10] Our study group showed similar increases in risk of MM (OR 1.25), but a greater risk of BCC (OR 1.49).

A prospective study conducted by Li et al focused on the Health Professionals' Follow-up Study Group for a 10-year period (2000-2010).[8] In this study, recent sildenafil use (within the past 3 month of skin cancer diagnosis) was associated with an increased risk of MM (HR 1.84). The Li study accounted for MM risk factors such as sun exposure, presence of moles, and family history; however, only 14 out of 142 cases of MM reported recent sildenafil use. In the Li study, there was almost no increased risk of BCC (HR 1.08) among sildenafil users in contrast to our findings with a much larger cohort.

A factor indicating causality is the presence of a dose-response relationship. Lian et al found minimal increased risk of developing MM among PDE5i users overall (HR 1.18) and found an increased risk of MM in those who had received 7 or more prescriptions for sildenafil (HR 1.34).[9] The mean number of PDE5i pills in our study for the PDE5i group was 11.8. To determine if a dose-response relationship was present, we analyzed incidence of skin cancers by quartiles of PDE5i use. Interestingly, we

found an overall OR of 1.25 for MM in PDE5i users with an increase in OR for the first 2 quartiles of pill counts of PDE5i users, an OR of 1.25 in the third quartile of PDE5i users and a decreased, and perhaps a protective effect (OR 0.81), in the fourth quartile of PDE5i users. PDE5i users in this group had >133 doses and a mean of 271 (standard deviation± 198) pill doses during the study period. Therefore, our results suggest a complex relationship between PDE5i exposure and MM risk. On the other hand, BCC risk was increased in all PDE5i users with OR of 1.49 and there appeared to be an increased risk with increasing pill counts among PDE5i users (OR 1.70 in fourth quartile of PDE5i users).

Pottegard et al found PDE5i users in the UK National Health System were more likely to utilize healthcare resources and have greater access to healthcare providers.[12] As a result, those patients were likely to have greater surveillance of common medical conditions, such as skin cancer. Similarly, we found PDE5i users had 8.9 VA outpatient clinic visits per year compared to 5.9 visits per year in the non-PDE5i group, suggesting more frequent visits to healthcare providers. More frequent visits to healthcare providers in the PDE5i group may be a possible explanation for the higher incidence of skin cancer in this group, but without measure of comorbidities in either group (including erectile dysfunction in the non-PDE5i group), this explanation is uncertain.

There are several limitations to our study that deserve discussion. These include retrospective design, no measure of sun exposure or sunscreen use, no record of family history of skin cancer, no record of skin type, no measurement of comorbidities (in either group), no measurement of erectile dysfunction in the comparison group, and inability to measure PDE5i drug use outside the VA healthcare system. In addition, we did not have access to the stage or grade of skin cancers in this study. In the PDE5i user group, we matched non-PDE5i users based on geographic location as defined by most frequently used VA facility. We also matched subjects based on age and race. This was an attempt to control for sun exposure in each group; however, we acknowledge and recognize the limitations of this method since we have no actual measure of sun exposure or other variables known to be associated with skin cancer risk. However, we believe the large number of subjects in each group and controlling for age, race, and geography would likely result in a random distribution of similar subjects with equal skin cancer risk in each group. Retrospective design has been the typical study design in this area of research and our study design is no different from others in this respect. Previous studies have included questionnaires about lifetime sun exposure and sunburns,[8] even though self-reported, historical data can be unreliable.

Our study design accounts for PDE5i drugs obtained in the VA healthcare system but did not account for PDE5i drugs that may have been obtained by these Veterans outside the VA system. This may have underestimated PDE5i exposure in the PDE5i users and nonuser groups. On the other hand, it has been shown 85% of Medicare eligible Veterans prescribed PDE5is obtain these medications exclusively from VA pharmacies while only 3% of Veterans taking these drugs were "dual" users (Medicare and VA eligible).[19] Based on this information, the higher cost of brand name PDE5is and practice experience of the authors, we believe a majority of Veterans PDE5i users in this study received their PDE5i prescriptions from the VA pharmacies.

Interestingly, we noted PDE5i users had increasing risk of BCC as pill counts increased with the highest OR of 1.70 found in the fourth quartile of PDE5i users. BCC along with MM is known to be increased in sun exposed areas of skin. It is possible that PDE5i users may spend more time in the sun and protect their skin less than non-PDE5i users although this question is not addressed in the current study. Additionally, it is not known whether the PDE5i drug class exerts an effect at a molecular or cellular level that increases the risk of BCC. These questions remain to be answered and warrant future research.

Our data set is the largest to date examining the relationship between PDE5i use and skin cancers. Based on our study results, the association of MM and BCC with PDE5i use is statistically significant due to the large number of subjects in each group, but the clinical significance of these findings is uncertain. Our results also suggest a possible protective effect against MM in higher level PDE5i users, which seems to contradict findings in previous studies as well as in vitro models. Considering these findings, it is likely other confounding variables are involved.

CONCLUSION

Veterans who received PDE5iS show a slight increase in risk of developing MM of the skin, but other confounding variables are likely involved. A direct relationship between PDE5i exposure and MM is questionable based on our study results. The risk of developing basal cell carcinoma of the skin appears to increase with increasing PDE5i exposure. PDE5i drugs remain a safe treatment for erectile dysfunction. Further study of PDE5i use and its relationship to skin cancers in a prospective fashion is warranted.

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